TSDR

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Case Studies in Environmental Medicine

16 Nitrate/Nitrite Toxicity

Environmental ALERT . . .

- ☑ ***Nitrate toxicity causes methemoglobinemia, which is a wholly preventable disease.***
- ☑ ***Infants less than 4 months of age are at particular risk of nitrate toxicity from contaminated water.***
- ☑ ***The widespread use of nitrate fertilizers increases the risk of well-water contamination in rural areas.***

This monograph is one in a series of self-instructional publications designed to increase the primary care provider's knowledge of hazardous substances in the environment and to aid in the evaluation of potentially exposed patients. See page 21 for more information about continuing medical education credits and continuing education units.

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U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

ATSDR

How to use this issue...

This issue begins with a composite case study that describes a realistic encounter with a patient. This description is followed by a pretest. The case study is further developed through Challenge questions at the end of each section. To benefit fully from this monograph, readers are urged to answer each question when it is presented. (Answers to the Pretest and Challenge questions are found on page 18.) The monograph ends with a posttest, which can be submitted to the Agency for Toxic Substances and Disease Registry (ATSDR) for continuing medical education (CME) credit or continuing education units (CEU). See page 21 for further instructions on how to receive these credits.

The objectives of this monograph on nitrates/nitrites are to help you:

- ❑ **Explain why nitrates/nitrites may be an acute and chronic health hazard**
- ❑ **Describe the known factors contributing to nitrate/nitrite toxicity**
- ❑ **Assess a patient's environmental or occupational exposure to nitrates/nitrites**
- ❑ **Evaluate and treat nitrate/nitrite exposure**
- ❑ **List sources of information on nitrates/nitrites**

Contents

This issue is prepared with the assistance of those who share a common concern for physician education, public health, and the environment, including the following organizations: American Academy of Family Physicians (AAFP), American Academy of Pediatrics (AAP), American College of Emergency Physicians (ACEP), American College of Occupational Medicine (ACOM), American Medical Association (AMA), Association of State and Territorial Health Officials (ASTHO), and the Society of Teachers of Family Medicine (STFM). Final responsibility for the contents and views expressed in this monograph resides with ATSDR.

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Case Study

A 2-month-old infant with vomiting, diarrhea, tachypnea, and cyanosis

A 2-month-old female infant is brought to your clinic in a rural area for a routine well-baby checkup. According to the child's chart, she was delivered 2 weeks early because of maternal toxemia. There was no neonatal distress; her birth weight was 7 pounds and 11 ounces.

Today, the mother states that she has noticed an intermittent bluish discoloration of the baby's lips, tip of the nose, and ears. Physical examination of the infant is negative for both cardiac murmurs and abnormalities on lung auscultation. A below-average weight gain is noted. Feedings have been 4 ounces of diluted formula every 2 hours. The infant has occasional loose stools. You instruct the parents to increase caloric feedings with vitamin and mineral supplements and to call you immediately if any further episodes of the bluish discoloration are observed.

Approximately 3 weeks later, the baby's frantic parents call your office; the infant is crying incessantly and has vomiting and profuse diarrhea. When the baby is brought to your clinic a few minutes later, she is afebrile but has tachypnea, cyanosis, and drowsiness. Her blood pressure is 78/30 mm Hg (normal 50th percentile for her age is 80/46 mm Hg), heart rate is 140/min, and respiration rate is 40/min. An ambulance is summoned and 100% oxygen by face mask is administered; however, no improvement in the cyanosis is noted on her arrival at the hospital emergency department.

The examining emergency physician now notes a grade II/VI systolic murmur and central cyanosis, which has not improved despite administration of 100% oxygen for nearly 1 hour. There is no evidence of cardiac failure, atelectasis, pneumonitis, or pneumothorax. Therapy is started, which results in a dramatic resolution of the cyanosis. The infant is discharged on the second hospital day with no evidence of central nervous system hypoxic damage.

(a) What was the most likely cause of this infant's cyanosis?

(b) What laboratory tests, either obtained during the hospitalization or ordered subsequently, would assist in confirming the diagnosis?

(c) What steps, if any, can be taken to prevent a recurrence of cyanosis and distress in this infant?

Answers can be found on page 18.

Exposure Pathways

- **Shallow, rural domestic wells are most likely to be contaminated with nitrates, especially in areas where nitrogen-based fertilizers are in widespread use.**
- **Other nitrate sources in well water include seepage from septic sewer systems.**
- **Foodstuffs contaminated with nitrites and sausage preserved with nitrates and nitrites have caused symptomatic methemoglobinemia in children.**
- **Deliberate abuse of volatile nitrite inhalants can cause severe methemoglobinemia and death.**

Nitrate (NO_3^-) and nitrite (NO_2^-) are naturally occurring inorganic ions, which are part of the nitrogen cycle. Wastes containing organic nitrogen are decomposed in soil or water by microbial action to first form ammonia, which is then oxidized to nitrite and nitrate. Because nitrite is easily oxidized to nitrate, it is nitrate that is predominantly found in groundwater and surface waters. Contamination with nitrogen-containing fertilizers, including anhydrous ammonia as well as animal or human natural organic wastes, can raise the concentration of nitrate in water. Nitrate-containing compounds in the soil are generally soluble and readily migrate with groundwater.

In agricultural areas, nitrogen-based fertilizers are a major source of contamination for shallow groundwater aquifers that provide drinking water. A 1990 Environmental Protection Agency (EPA) survey found that about 1.2% of community wells and about 2.4% of rural domestic wells had nitrate concentrations in excess of federal regulatory limits. (see page 15) A similar survey conducted in Iowa indicated that about 18.3% of rural domestic wells contained concentrations of nitrate above the regulatory level. Other sources of nitrate contamination are organic animal wastes and contamination from septic sewer systems, especially in wells less than 100 feet deep. During spring melt or drought conditions, both domestic wells and public water systems using surface water may have increased nitrate concentrations.

Although vegetables are seldom a source of acute toxicity, they account for more than 70% of the nitrates in a typical human diet. Cauliflower, spinach, collard greens, broccoli, and root vegetables have a naturally greater nitrate content than other plant foods. The remainder of the nitrate in a typical diet comes from drinking water (about 21%) and from meat and meat products (about 6%) in which sodium nitrate is used as a preservative and color-enhancing agent.

Symptomatic methemoglobinemia has occurred in children who have eaten sausage heavily treated with nitrates and nitrites. For infants, the major source of nitrate exposure is drinking water used to dilute formula.

Accidental exposure to nitrites in chemical laboratories and ingestion in suicide attempts have been described. Deliberate abuse of volatile nitrites (amyl, butyl, and isobutyl nitrites) as psychedelics or aphrodisiacs occurs widely; these agents are known by street names such as "snappers," "poppers," "Locker Room," and "Rush."

Nitrate or nitrite exposure also may occur from certain medications. Infants and children are especially susceptible to nitrate exposure through topical silver nitrate used in burn therapy. Other medications implicated in cases of nitrate or nitrite toxicity are quinone derivatives (antimalarials), nitroglycerine, bismuth subnitrite (antidiarrheal), ammonium nitrate (diuretic), amyl and sodium nitrites (antidotes for cyanide and hydrogen sulfide poisoning), and isosorbide dinitrate/tetranitrates (vasodilators used in coronary artery disease therapy). (See Table 1.)

Sodium nitrite used as an anticorrosive agent in cooling fluids, ammonium nitrate found in cold packs, and nitrous gases used in arc welding are other possible sources of exposure. An ethyl nitrite folk remedy called "sweet spirits of nitre" has caused fatalities. Serious poisoning and death have occurred when sodium nitrate was mistaken for table salt and ingested with food.

Table 1. Reported inducers of methemoglobinemia

AGENT	SOURCE/USE
Inorganic nitrates/nitrites	Contaminated well water
	Meat preservatives
	Vegetables—carrot juice; spinach
	Silver nitrate burn therapy
	Industrial salts
	Contaminants of nitrous oxide canisters for anesthesia
Organic nitrites	
Butyl/isobutyl nitrite	Room deodorizer propellants
Amyl nitrite	Inhalant in cyanide antidote kit
Nitroglycerine	Oral, sublingual, or transdermal pharmaceuticals for treatment of angina
Others	
Aniline/aminophenols	Laundry ink
Nitrobenzene	Industrial solvents; gun-cleaning products
Local anesthetics	Benzocaine; lidocaine; Propitocaine®; Prilocaine®
Sulfonamides	Antibacterial drugs
Phenazopyridine	Pyridium®
Antimalarials	Chloroquine®; Primaquine®
Sulfones	Dapsone®
p-Aminosalicylic acid	Bactericide (tuberculostatic)
Naphthalene	Mothballs
Copper sulfate	Fungicide for plants, seed treatment
Resorcinol	Antiseborrheic, antipruritic, antiseptic
Chlorates	Matches, explosives, pyrotechnics
Combustion products	Fires

Adapted from: Dabney BJ, Zelarney PT, Hall AH. Evaluation and treatment of patients exposed to systemic asphyxiants. Emergency Care Quarterly 1990;6(3):65-80.

Challenge

(1) What questions will you ask the parents of the infant in the case study to help determine the cause of the cyanosis?

(2) If well water used to dilute formula is implicated in the cyanosis, what are some possible causes of its nitrate contamination?

Who's at Risk

- **Infants less than 4 months of age are at the greatest risk for nitrate toxicity.**
- **About 1% to 2% of the U.S. population that uses drinking water from public water systems may be exposed to nitrates in excess of the EPA-recommended maximum concentration.**

Infants less than 4 months of age who are fed formula diluted with water from rural domestic wells are especially prone to developing acute acquired methemoglobinemia from nitrate exposure. The pH of the gut is normally higher in infants than in older children and adults. Higher gut pH enhances the conversion of ingested nitrate to more potent nitrite; gastroenteritis with vomiting and diarrhea can exacerbate nitrite formation.

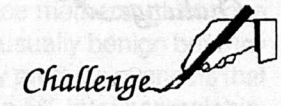
A large proportion of hemoglobin in infants is in the fetal hemoglobin form, which is more readily oxidized by nitrites to methemoglobin than adult hemoglobin is. In infants, NADH*-dependent methemoglobin reductase, the enzyme responsible for reduction of methemoglobin back to normal hemoglobin, has only about half the activity present in adults. These factors combine to place young infants who are fed formula diluted with nitrate-contaminated well water at the greatest risk of toxicity. There is little evidence that breast-fed infants develop methemoglobinemia from exposure to nitrates ingested by the nursing mother.

* Reduced form of nicotinimide adenine dinucleotide

The first reported case of fatal acquired methemoglobinemia in an infant due to ingestion of nitrate-contaminated well water occurred in 1945. Since that time about 2,000 similar cases of acquired methemoglobinemia in young infants have been reported worldwide; about 10% of such cases result in fatality. The most recently reported U.S. case of infant mortality due to this source was in 1987.

In pregnant women, the level of methemoglobin increases from the normal (0.5% to 2.5% of total hemoglobin) to a maximum of 10.5% at the 30th week of pregnancy and subsequently declines to normal after delivery. Thus, pregnant women may be more sensitive to the induction of clinical methemoglobinemia by nitrites or nitrates at or near the 30th week of pregnancy.

It has been estimated that 1% to 2% of the U.S. population using drinking water from public water systems may be consuming nitrates in excess of the EPA-recommended maximum concentration. It has also been estimated that residents in as many as 603,000 homes consume drinking water from nitrate-contaminated domestic wells. Although suppliers of public water sources are required to monitor nitrate concentrations regularly, rural wells often are not routinely tested for nitrates.



(3) What recommendations can you make to the infant's family in the case study to prevent further cyanotic episodes?

Biologic Fate

- **In vivo conversion of nitrates to nitrites significantly enhances nitrates' methemoglobin-inducing potency.**
- **Nitrates are excreted rapidly in the urine.**

In humans, ingested nitrate is rapidly absorbed from the proximal small bowel and distributed throughout the body. Nitrate then enters the large bowel from the blood, where it is rapidly converted to highly reactive nitrite, in part by fecal microorganisms. The formed nitrite is reabsorbed into the blood, where it reacts with the ferrous (Fe^{2+}) iron of deoxyhemoglobin, forming methemoglobin with iron in the ferric (Fe^{3+}) valence state. Ferric iron is unable to transport oxygen.

Nitrates are rapidly converted in the liver to denitrated metabolites and inorganic nitrites, which are then excreted in urine. Approximately 60% to 70% of an ingested nitrate dose is excreted in urine within the first 24 hours. About 25% is excreted in saliva through an active blood nitrate transport system and potentially is reabsorbed. Half-lives of parent nitrate compounds are usually less than 1 hour; half-lives of metabolites range from 1 to 8 hours.

Challenge

(4) What factors make infants less than 4 months of age more susceptible to developing methemoglobinemia when exposed to nitrates?

Physiologic Effects

Unless favorable conditions exist for reducing nitrate to nitrite in the gut (i.e., high pH, proper intestinal microbial flora), ingested nitrate (NO_3^-) is metabolized and excreted without producing apparent adverse effects. The effects of nitrite (NO_2^-) are the same whether nitrite-containing compounds are ingested or inhaled, or nitrite is produced in vivo from nitrate.

Hematologic Effects

The principal mechanism of nitrite toxicity is the oxidation of the ferrous iron (Fe^{2+}) in deoxyhemoglobin to the ferric (Fe^{3+}) valence state, producing methemoglobin. Methemoglobin cannot reversibly bind or transport circulating oxygen. Depending on the percentage of total methemoglobin in oxidized form, the clinical picture is one of oxygen deprivation with cyanosis, cardiac dysrythmias and circulatory failure, and progressive central nervous system (CNS) effects. The CNS effects may range from mild dizziness and lethargy to coma and convulsions.

- **Acute acquired methemoglobinemia is the most important adverse health effect caused by excessive nitrate exposure.**
- **Some methemoglobin-inducing agents can also cause Heinz body hemolytic anemia or sulfhemoglobinemia.**

Hemoglobin protein may also be oxidized, causing denaturation and erythrocyte hemolysis and resulting in hemolytic anemia. The denatured protein is visible on special peripheral blood stains as Heinz bodies (minute bodies sometimes seen in erythrocytes by the dark illumination method). Many agents that induce methemoglobin can also induce a sulfhemoglobinemia, which is usually benign but may confound the diagnosis. Sulfhemoglobin may produce cyanosis that is apparent at concentrations as low as 3% to 5% total hemoglobin.

Two enzymes (one NADH-dependent, the other NADPH-dependent) are normally present that reduce methemoglobin back to hemoglobin. A physiologic methemoglobinemia (1% to 2% of total hemoglobin) is typical in humans as a result of exposure to oxidizing substances and diet. A rare *congenital methemoglobinemia* (10% to 50% of total hemoglobin) may be found in persons with either hemoglobin M disease* or a deficiency of NADH-dependent methemoglobin reductase. *Acquired methemoglobinemia* is caused by exposure to oxidizing substances including nitrates and nitrites. Persons with a deficiency of NADH-dependent reductase may be more susceptible to developing symptomatic methemoglobinemia after exposure to nitrates and nitrites.

* A disease caused by a group of abnormal hemoglobins in which a single amino acid substitution favors the formation of methemoglobin, in spite of normal quantities of methemoglobin reductase.

Cardiovascular Effects

- **Hypotension, shock, and cardiac arrhythmias may occur in cases of severe methemoglobinemia.**

In large doses, nitrite is an excellent vasodilator due to its relaxing action on vascular smooth muscle; hypotension and shock can result. Systolic flow murmurs may be heard on auscultation in persons with severe methemoglobinemia, which may develop with too-rapid intravenous administration of sodium nitrite (used as an antidote for cyanide and hydrogen sulfide poisoning) or sodium nitroprusside (used in hypertensive crisis therapy). In patients who have inhaled volatile nitrites, transient electrocardiographic changes (T-wave inversions and ST-segment depression) may be noted.

Respiratory Effects

- **Severe methemoglobinemia may lead to metabolic acidosis.**

Metabolic acidosis develops in cases of severe methemoglobinemia, especially in young infants or when hypotension and shock are present. Dyspnea and tachypnea are common findings in patients with significant methemoglobinemia. Respiratory tract irritation may occur in patients who abuse volatile nitrites.

Other Effects

- **Chocolate-brown cyanosis is a hallmark of methemoglobinemia.**

A chocolate-brown or slate-gray central cyanosis (involving the trunk and proximal portions of the limbs, as well as the distal extremities and mucous membranes) is one of the hallmarks of methemoglobinemia. This cyanosis is due to the dark chocolate-brown color of methemoglobin itself and usually becomes noticeable at a concentration of 10% to 15% of total hemoglobin.

Concern has been expressed about the cancer-causing potential of nitrates and nitrites used as preservatives and color-enhancing agents in meats. Nitrates can react with amino acids to form nitrosamines, which have been reported to cause cancer in animals. However, data from human and experimental animal studies have failed to provide conclusive evidence that nitrate or nitrite ingestion causes carcinogenic or teratogenic effects.

Clinical Evaluation

History and Physical Examination

❑ **Cyanosis that fails to improve with administration of 100% oxygen is a sentinel finding in cases of methemoglobinemia.**

Evaluation of a patient with suspected nitrate/nitrite exposure includes a complete medical history and physical examination. Clues to potential exposure are often obtained by reviewing the following items with the patient or family:

- Location of dwelling (urban, suburban, rural)
- Drinking water source and supply (in case of well water: depth, location, type of well construction, and frequency of microbiologic and nitrate testing)
- Surrounding activities (agricultural, industrial) and proximity to drinking-water source
- Type of sewer system (municipal, septic) and proximity to drinking-water source
- Occupations, avocations, and hobbies of family members
- Nutritional status (for infants: type of formula, feeding regimen, and source of dilution water)
- Family history, including recent use of medications by infant and mother
- History of recent gastroenteritis with vomiting or diarrhea

Physical examination should include special attention to the color of the skin and mucous membranes. If a history of gastroenteritis is present (especially in infants), evaluate the patient for the possible presence of dehydration (poor skin turgor, sunken fontanelle, dry mucous membranes). All cyanotic patients should be assessed for possible cardiac and lung disease (cardiac murmurs, gallops, arrhythmias; rales, rhonchi, wheezes, dullness or hyperresonance in the chest). A central chocolate-brown or slate-gray cyanosis that does not respond to administration of 100% oxygen is indicative of methemoglobinemia; cyanosis due to cardiorespiratory compromise most often improves with administration of 100% oxygen.

In young infants, look for labored breathing, respiratory exhaustion, hypotension, below-average weight gain, and failure to meet developmental milestones. Gastroenteritis can increase the rates of production and absorption of nitrites in young infants and aggravate methemoglobinemia.

Signs and Symptoms

Signs and symptoms of methemoglobinemia can be directly correlated with the percentage of total hemoglobin in the oxidized form (Table 2).

Signs and symptoms of methemoglobinemia are related to the percentage of oxidized hemoglobin in the blood.

Table 2. Signs and symptoms of methemoglobinemia

Methemoglobin concentration	Clinical findings
10%-20%	Central cyanosis of limbs/trunk; usually asymptomatic
20%-45%	CNS depression (headache, dizziness, fatigue, lethargy, syncope), dyspnea
45%-55%	Coma, arrhythmias, shock, convulsions
>70%	High risk of mortality

From: Dabney BJ, Zelarney PT, Hall AH. Evaluation and treatment of patients exposed to systemic asphyxiants. Emergency Care Quarterly 1990;6(3):65-80.

The lips and mucous membranes of patients with nitrate/nitrite toxicity usually have more of a brownish than a bluish cast. Dyspnea, especially on exertion, is common. Varying degrees of central nervous system depression may be present. The cardiac and pulmonary examinations are usually normal, but systolic flow murmurs may be detected. Cardiac arrhythmias and hypotension may occur in patients with severe poisoning, although death from methemoglobinemia alone is uncommon, except in infants.

Laboratory Evaluation

Most commonly, a drop of the patient's blood is placed on a piece of filter paper alongside a drop of blood from a normal individual; when dry, the methemoglobin-containing blood will turn a deep chocolate-brown or slate-gray color in comparison. A tube of methemoglobin-containing blood will not turn red when shaken in air or when oxygen is bubbled through it; whereas blood that is dark because of a high content of normal deoxyhemoglobin will turn red.

Methemoglobinemia results in distinct changes in blood color and oxygen-carrying capacity.

Screening Tests

- Examination of blood color
- Determination of the calculated versus measured arterial saturation gap
- Hemoglobin and hematocrit
- Serum-free hemoglobin (for hemolysis detection)
- Serum haptoglobin (for hemolysis detection)
- Heinz bodies on peripheral blood smear
- Urinalysis

Specialized Tests

- Determination of methemoglobin level
- Tests for causes of congenital methemoglobinemia:
  - — Hemoglobin electrophoresis
  - — Activity of NADH-dependent methemoglobin reductase
- Tests for causes of failure of methylene blue therapy (see Treatment and Management, page 13):
  - — Activity of glucose-6-phosphate dehydrogenase (G-6-PD)
  - — Activity of NADPH-dependent methemoglobin reductase
  - — Sulfhemoglobin blood level (not readily available for clinical use)

Direct Biologic Indicators

❑ **Measurements of nitrates or nitrites in blood, urine, or saliva are not clinically useful.**

Although 80% to 90% of the body's excretion of nitrate is through urine and saliva, biologic nitrate or nitrite levels are generally not useful for diagnostic purposes. However, urinary and salivary nitrate concentrations can be important indicators of exposure requiring remedial action. The correlation between blood nitrite and methemoglobin is not usually linear at lower nitrite concentrations since a certain minimum amount of nitrite must enter the bloodstream before a measurable increase in methemoglobin concentration can be detected.

Indirect Biologic Indicators

❑ **The most useful diagnostic test for nitrate toxicity is a blood methemoglobin level.**

❑ **Percent O_2 saturation is an important but nonspecific finding in patients with methemoglobinemia.**

The methemoglobin level in blood is the most useful screening, as well as diagnostic, test for nitrate toxicity. Methemoglobin can be measured in whole blood using a visible spectrophotometer (or Co-Oximeter) at 635 nanometers. To express the methemoglobin level as a percentage, total hemoglobin content of the blood sample also must be determined. Oximeters used to measure methemoglobin levels may falsely report sulfhemoglobin as methemoglobin. Although sulfhemoglobinemia is seldom severe enough to be life-threatening,

its presence can explain some methylene blue treatment (see Treatment and Management, page 13) failures. For the evaluation of suspected congenital methemoglobinemia, hemoglobin electrophoresis is helpful.

In patients with methemoglobinemia, the partial pressure of oxygen (pO_2) is usually normal despite the presence of an abnormal hemoglobin that cannot bind or transport oxygen. The percent O_2 saturation calculated by some blood-gas instruments from the pO_2, or calculated manually with a nomogram, will be normal. However, the percent O_2 saturation actually measured with a Co-Oximeter will be decreased, resulting in a calculated versus measured arterial "percent O_2 saturation gap." This finding is not specific for methemoglobinemia, however, since carboxyhemoglobinemia and sulfhemoglobinemia produce the same findings.

Percent O_2 saturation determined with a pulse oximeter may be unreliable in patients with methemoglobinemia, especially after administration of methylene blue (see Treatment and Management, page 13). Arterial blood gases should be used to monitor oxygenation in such patients.

Environmental Indicators

In young infants, drinking water is the most common source of nitrate exposure. Water tests for nitrate can be obtained from any public health laboratory that utilizes approved EPA procedures. Care should be taken to compare the results to the reference units provided by the laboratory. Some laboratories report nitrate levels as milligrams per liter (mg/L) nitrate; others report nitrate levels as mg/L nitrate-nitrogen (NO_3-N).

- **Since drinking water is the most common source of nitrates, testing the water supply of patients with a suspected exposure is prudent.**

Challenge

(5) In addition to methemoglobinemia, what other clinical conditions may occur from exposure to methemoglobin-inducing substances?

_____

_____

(6) What laboratory tests are useful for evaluating a patient with suspected methemoglobinemia?

_____

_____

Treatment and Management

- **Methylene blue is an effective antidote for most patients with methemoglobinemia.**

- **Treatment alone is insufficient; the nitrate source must be identified and eliminated from the patient's environment.**

In cases of mild nitrate toxicity (blood methemoglobin levels less than 20%), asymptomatic patients do not require treatment other than avoiding ingestion or inhalation of substances that cause methemoglobinemia. In symptomatic patients with moderate or severe toxicity and hypoxia or dyspnea, 100% oxygen should be administered immediately to fully saturate all remaining normal hemoglobin.

Specific therapy for methemoglobinemia consists of intravenous administration of methylene blue at a dose of 1 to 2 milligrams/kilograms (mg/kg) body weight (0.1 to 0.2 milliliters [mL]/kg body weight of a 1% solution in saline) over a 5-to10-minute period. Within 15 minutes of methylene blue administration, cyanosis will usually begin to improve obviously. If no response to the initial injection has occurred within 15 minutes in seriously ill patients, or within 30 to 60 minutes in moderately ill patients, a second methylene blue dose of 0.1 mL/kg body weight may be given. Caution is advised since methylene blue can slightly worsen methemoglobinemia when given in excessive amounts. In general, the total dose administered during the first 2 to 3 hours should not be greater than 0.5 to 0.7 mL/kg of body weight.

Methylene blue should not be administered to a patient with known G-6-PD deficiency, as severe hemolytic anemia may develop.

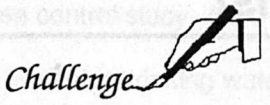
For severe, life-threatening methemoglobinemia, especially when the patient responds poorly to methylene blue therapy or when the patient is known to have G-6-PD deficiency, treatment options include exchange transfusion and hyperbaric oxygen therapy. During treatment in the hyperbaric chamber, sufficient oxygen can be dissolved directly in the blood to support life; reversible binding to hemoglobin is not required.

Blood transfusion may be required if massive hemolysis develops. In persons with severe hemolysis, maintaining a brisk urine flow and alkalinizing the urine by administration of sodium bicarbonate may help protect against renal injury from erythrocyte breakdown products.

Patients with severe poisoning who are experiencing seizures or cardiac arrhythmias may require anticonvulsant or antiarrhythmic therapy. If a local anesthetic is suspected of being the etiologic agent for the methemoglobinemia, however, lidocaine probably should be avoided.

Treatment alone is not adequate for nitrate poisoning. The patient and the nitrate source must be permanently separated. In the case of infantile acquired methemoglobinemia, well water used in preparing formula is a primary etiologic suspect. Physicians and community health personnel should be aware that high nitrate levels in water supplies may suggest the presence of bacterial contamination or agricultural chemicals, which might have serious consequences, especially for infants and pregnant women (increased methemoglobin sensitivity), as well as potential fetal risk. The conventional approach of boiling water to destroy microorganisms is not a safe practice when nitrate contamination is suspected; evaporation actually increases the nitrate concentration.

Alternative sources of uncontaminated water may include water from a well that has been tested and found to have an acceptable nitrate content, bottled water, water from a new and deeper well, or water from a regularly monitored public water supply. Water treatment technologies (ion exchange resins or reverse osmosis) to remove nitrate from water are not adequate to remove other associated contaminants, especially coliform bacteria. Private wells should be tested for nitrate concentration annually.



(7) Why might some patients with methemoglobinemia not respond to treatment with methylene blue?

_____

_____

(8) What options are available to treat significant methemoglobinemia in a patient known to have G-6-PD deficiency?

_____

_____

Standards and Regulations

The nitrate limit in drinking water was established as a safeguard against infantile acquired methemoglobinemia. The EPA regulations require the nitrate content of potable water to be below 45 mg/L (45 parts per million [ppm]) measured as nitrate (NO_3^-) or 10 mg/L (10 ppm) measured as nitrogen in nitrate (NO_3-N).

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Related Government Documents

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National Academy of Sciences. The health effects of nitrite, nitrate and N-nitroso compounds. Washington, DC: National Academy Press, 1981.

Sources of Information

More information on the adverse effects of nitrates/nitrites and treating and managing cases of exposure to nitrates/nitrites can be obtained from ATSDR, your state and local health departments, and university medical centers. *Case Studies in Environmental Medicine: Nitrate/Nitrite Toxicity* is one of a series. For other publications in this series, please use the order form on the back cover. For clinical inquiries, contact ATSDR, Division of Health Education, Office of the Director, at (404) 639-0730.

Answers to Pretest and Challenge Questions

Pretest

Pretest questions are on page 1.

(a) In an infant, cyanosis that is unresponsive to oxygen therapy is most likely due to methemoglobinemia.

(b) The clinical laboratory tests that will confirm the diagnosis of methemoglobinemia are blood color and arterial blood gases. When a drop of methemoglobin-containing blood is placed on filter paper, it dries a deep chocolate-brown or slate-gray color. The level of methemoglobin in the blood can be measured using a Co-Oximeter. Analysis of arterial blood gases will reveal normal oxygen pressure.

In the case of infantile acquired methemoglobinemia, well water used to prepare formula should be tested for the presence of nitrates. Ingestion of nitrate-containing water is not an uncommon cause of methemoglobinemia in infants, especially those residing in rural areas.

(c) The initial step in preventing a recurrence of the infant's cyanosis and distress is to identify the cause of the infant's cyanosis; the next step is to correct or eliminate the cause. If the infant is suffering from acquired methemoglobinemia, the agent must be identified and removed from the infant's environment.

Challenge

Challenge questions begin on page 4.

(1) Questions that may help define the cause of the cyanosis include dwelling location; surrounding activities; type of sewer system; occupations, avocations, and hobbies of family members; drinking water source and supply; in infants, the type of formula, feeding regimen, and source of dilution water; family history, including recent use of all medications by both infant and mother; and in infants, a history of recent gastroenteritis.

(2) Causes of high nitrate concentrations in well water include runoff from the use of nitrogen-containing agricultural fertilizers (including anhydrous ammonia) and seepage of organic nitrogen-containing material from animal wastes or septic sewer systems.

(3) The well water should be tested for nitrate concentration and presence of coliform bacteria. It is most important to identify the source of the methemoglobin-inducing agent and to preclude any further exposure to the infant. If nitrate-contaminated well water is the source, utilizing bottled or other uncontaminated water to dilute formula should be recommended.

You could also recommend frequent testing of the well for nitrate concentration and bacterial contamination, or drilling a new and deeper well, taking into consideration the proximity of septic sewer systems, location of animal wastes, and proximity to agricultural land that may be regularly treated with nitrogen-based fertilizers.

(4) Infants less than 4 months of age are more susceptible to developing methemoglobinemia because the pH of the gut is normally higher than in older children and adults, which enhances the conversion of ingested nitrate to the more potent nitrite. The bacterial flora of the young infant's gut is also different from that found in older children and adults and may be more likely to convert ingested nitrate to nitrite. Gastroenteritis can increase both the in vivo transformation of nitrate to nitrite and the systemic absorption of nitrite from the large intestine.

A large proportion of hemoglobin in young infants is in the form of fetal hemoglobin. Fetal hemoglobin is more readily oxidized to methemoglobin by nitrites than is adult hemoglobin. Also, in infants, NADH-dependent methemoglobin reductase, the enzyme responsible for reduction of induced methemoglobin back to normal hemoglobin, has only about half the activity present in adults.

(5) Hemolytic anemia or sulfhemoglobinemia can be caused by many substances that induce methemoglobinemia.

(6) The level of methemoglobinemia can be measured with a Co-Oximeter. Although biologic nitrate and nitrite levels can be determined, these tests are not routinely performed; it is more expedient to identify and measure nitrate at its source (e.g., contaminated well water).

If congenital methemoglobinemia is suspected or if the patient responds poorly to treatment with methylene blue, the following tests should be performed: hemoglobin electrophoresis, G-6-PD activity, and the activities of NADH- and NADPH-dependent methemoglobin reductases.

(7) Some patients may not respond to methylene blue treatment because they have a G-6-PD deficiency, sulfhemoglobinemia, or hemoglobin M disease.

(8) Treatment options for patients with G-6-PD deficiency include exchange transfusion and hyperbaric oxygen therapy.

Posttest

Continuing education credit is available to health professionals who use this monograph and complete the posttest. The criterion for awarding CME credits and CEUs is a posttest score of 70% or better.

The Agency for Toxic Substances and Disease Registry, in joint sponsorship with the Centers for Disease Control (CDC), is offering 1 credit hour of continuing medical education (CME) credit in category 1 of the Physician's Recognition Award of the American Medical Association and 0.1 hour of continuing education units (CEU) for other health professionals upon completion of this monograph.

The CDC is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to sponsor continuing medical education for physicians, and by the Council on the Continuing Education Unit (CCEU) to sponsor continuing education units for other health professionals.

This program has been reviewed and is acceptable for 1 prescribed hour by the American Academy of Family Physicians (term of approval: beginning January 1992). For specific information, please consult the AAFP Office of Continuing Medical Education.

The American College of Emergency Physicians (ACEP) has approved this program for 1 hour of ACEP Category 1 credit.

The American Osteopathic Association (AOA) has approved this program for 1 credit hour of Category 2-B AOA-CME credit.

To receive continuing education credit (CME or CEUs), complete the Posttest on page 22 in the manner shown in the sample question below. **Circle all correct answers.**

Which of the following is known to precipitate migraine headaches?

(a) fatigue
(b) alcohol
c. grapefruit
(d) sunlight
e. sleep

After you have finished the Posttest, please transfer your answers to the answer sheet on the inside back cover and complete the evaluation on the lower half of that page. Fold, staple, and mail the back cover to Continuing Education Coordinator, Agency for Toxic Substances and Disease Registry, Division of Health Education, E33, 1600 Clifton Road, Atlanta, GA 30333. Your confidential test score will be returned with an indication of where the correct answers can be found in the text. Validation of earned CME credit and CEUs will also be forwarded to participants, and their names, if requested, will be placed on the mailing list to receive other issues in the *Case Studies in Environmental Medicine* series.

POSTTEST: NITRATES/NITRITES

Circle **all** correct answers and transfer your answers to page 23.

1. Which of the following subpopulations are most at risk of adverse effects from nitrate exposure?
   a. pregnant women
   b. telephone line workers
   c. newborn infants
   d. infants less than 4 months of age
   e. fetuses
2. Which of the following are possible sources of nitrate exposure?
   a. certain topical burn medications
   b. shallow domestic wells in rural areas
   c. meat preservatives
   d. seepage from septic tanks
   e. freezer cold packs
3. Which of the following statements about nitrates are true?
   a. Nitrates can be converted to nitrites in the gut.
   b. The higher alkalinity of an infant's gut protects it from nitrate toxicity.
   c. Vomiting and diarrhea can affect the absorption of nitrites.
   d. No case of nitrate poisoning has been reported since 1950.
   e. Adults are immune from nitrate toxicity if they drink water from public water systems.
4. Methemoglobinemia may be induced by which of the following?
   a. chloroquine
   b. lidocaine
   c. nitroglycerine
   d. chlorates
   e. sulfonamides
5. Which of the following statements are true regarding nitrates?
   a. Rapid conversion of nitrates to nitrites occurs mainly in red blood cells.
   b. Fecal organisms convert nitrites back to nitrates, thereby protecting adults from toxicity.
   c. Nitrites react with deoxyhemoglobin to form Fe^{3+}.
   d. Most of an ingested dose is excreted in the urine and saliva.
   e. Boiling contaminated water will quickly rid it of nitrates.
6. Which of the following may be adversely affected by nitrates?
   a. cardiovascular system
   b. skin
   c. pulmonary system
   d. hematologic system
   e. fetal development
7. Which of the following statements are true?
   a. Signs and symptoms of methemoglobinemia are roughly correlated with % oxidized hemoglobin.
   b. Fetal hemoglobin is more readily oxidized by nitrites than is adult hemoglobin.
   c. Methemoglobin causes arterial blood to be blue in color.
   d. Cardiac arrythmias and hypotension can result from severe nitrate poisoning.
   e. Blood methemoglobin level is the most useful diagnostic test for nitrate toxicity.
8. Which of the following treatments may be used for patients with nitrate toxicity?
   a. 100% oxygen
   b. methylene blue
   c. amyl nitrite
   d. nitroglycerine
   e. exchange transfusion

CASE STUDIES IN ENVIRONMENTAL MEDICINE: NITRATE/NITRITE TOXICITY

If you wish CME credits or CEUs, please indicate your answers to the Posttest questions on page 22 by circling the letters below for the correct answers. Complete the evaluation questionnaire and fill in the information requested on the reverse side. Tear off this last page, fold, staple, and mail to Continuing Education Coordinator, Agency for Toxic Substances and Disease Registry, Division of Health Education, E33, 1600 Clifton Road, Atlanta, GA 30333.

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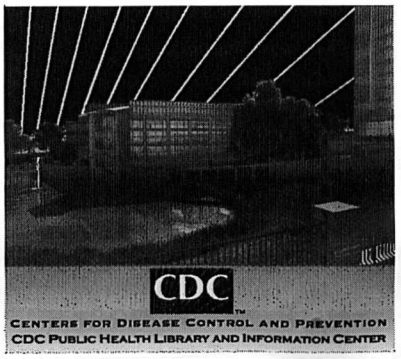

The state of knowledge regarding the treatment of patients potentially exposed to hazardous substances in the environment is constantly evolving and often uncertain. In this monograph, the Agency for Toxic Substances and Disease Registry (ATSDR) has made diligent effort to ensure the accuracy and currency of the information presented but makes no claim that the document comprehensively addresses all possible situations related to this substance. This monograph is intended as an additional resource for physicians and other health professionals in assessing the condition and managing the treatment of patients potentially exposed to hazardous substances. It is not, however, a substitute for the professional judgment of a health care provider and must be interpreted in light of specific information regarding the patient available to such a professional and in conjunction with other sources of authority.

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